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COMPLETE SPECIFICATION.

Coated Tablets.

We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to coated tablets and the coating which is used for protecting the tablet. More particularly this invention relates to a tablet having thereon a coating consisting of two layers; the inner or first layer comprising a sugar layer and the outer or top layer consisting of methylcellulose and a polyalkylene glycol.

Recent advances in the art of coating tablets are the film-coating and the air-suspension methods of coating tablets. However, as with most new advances certain disadvantages appear along with the innovations. The air-suspension machine coats the tablets by tumbling the tablets in air and blowing the coating solution onto the suspended tablets. The rapid agitation in the air currents necessary to suspend the tablets causes considerable damage to the tablets particularly due to abrasion. Another disadvantage of the air-suspension machine is the necessity for a volatile organic solvent in the coating composition to provide a rapid volatilization of the solvent and deposition of coating material. The film-forming materials generally also require a volatile organic solvent for the preparation of a solution. However, these volatile solvents are also generally good solvents for the drug in a tablet and there is a tendency for the active ingredient to be dissolved out of the tablet with concomitant loss thereof, roughening of the surface of the tablet and deposition of the active medicinal within the coating itself, thereby giving the coating a mottled appearance and a bad taste. It has now been found that tablets coated by the present invention are free from the above-mentioned disadvantages of the film coating and the air-suspension methods of coating and they possesses other advantages as hereinafter stated.

The present invention comprises a tablet coated with an inner layer consisting essentially of a sugar and an outer layer consisting essentially of methylcellulose and a polyalklene glycol.

The tablet coating of the present invention uniformly covers the tablets with a coating which protects against any disagreeable odor or taste of the medicament. The coating also is of high gloss and does not require a polishing operation, said high gloss being retained, even after handling and packaging operations. The coating is resistant to handling and high humidity conditions.

The First Layer or Inner Coat

The principal coating ingredient of the inner coat or layer is sugar, preferably sucrose. Other suitable sugars include lactose, maltose, fructose, glucose, and xylose. For the purposes of the present invention the sugar coating solutions known in the art for preparing sugar coatings are suitable. For example, aqueous solutions of 1-1/2 to 2-1/2 parts by weight of sucrose to 1 part by weight of water are satisfactory. As a general rule the more concentrated the sugar in solution the faster a coating can be applied. Higher

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concentrations of sugar can be obtained by heating the solution.

In addition to sugar, the coating can contain additional material as an adjuvant. For example, gelatin, sodium carboxymethylcellulose, hydroxyethylcellulose and preservatives can be added. Adjuvants, when added, can comprise up to 5% by weight of the coating solids.

The coating solutions are quite simply prepared by dissolving the solids in water, using heat if desired.

The first layer or inner coat is applied to the tablets by means of a standard tablet coating pan. The solutions can be ladled or sprayed on the tumbling tablets.

Between applications of the sugar coating syrups dusting agents can be added to facilitate the coating operation. Suitable dusting agents are, for example, calcium carbonate, calcium sulfate, talc and mixtures thereof. Additionally from 5 to 10% of acacia can be added to the dusting powder.

The Outer Layer or Topcoat

The principal film-forming ingredient of the outer layer is methylcellulose. As used in the specification and claims the term methylcellulose is used to mean the methyl ether of cellulose containing from about 24% to about 32% of methoxy. (—O—CH_3) groups; additionally, the term is used to include the cellulose derivatives which, in addition to the aforementioned methoxy groups, also contain from about 4% to about 12% of 2-hydroxypropoxyl groups. The methylcellulose is commercially available in a number of forms which differ in the degree of etherification. These forms are marketed with regard to the viscosity imparted to aqueous solutions. The low viscosity forms are preferred as it is possible to prepare coating solutions with a higher concentration of film-forming solids which permits the formation of a coating more quickly and with economy of solvents. The methylcellulose can be from about 50 to about 95% w/w of the top coating with from about 75 to 85% w/w being preferred.

The other principal ingredient of the outer layer is a polyalkylene glycol. Suitable polyalkylene glycols are polyethylene glycol and polypropylene glycol having an average molecular weight of from 200 to 9000. Their concentration can be from about 5 to about 50% w/w of the coating. It is preferred to use polyethylene glycol in a preferred concentration of from about 5 to about 25% w/w.

Additional minor ingredients in the outer coating can include adjuvants as coloring agents such as the non-toxic dyes, pigments and lakes which have been certified for use in the food, drug and cosmetic industry; flavoring agents to impart a pleasant taste, such as peppermint oil, oil of wintergreen, licorice and spearmint; sweetening agents such as cyclamate and saccharin; and opacifiers such as titanium dioxide and ferric oxide (Indian Red Oxide). Also reodorants such as vanilla and citrus to give a pleastant odor can be included.

The compositions are prepared by dissolving the methylcellulose and polyethylene glycol in a suitable volatile solvent, or preferably in a system of two or more miscible co-solvents. In the preferred solvent system, a solution of chloroform, methanol and water is used in a ratio by weight of 55 parts chloroform, 35 parts methanol and 10 parts water. The water can be omitted from the foregoing solvent system if desired. Additional suitable organic volatile solvents wrich can be used include methylene chloride, ethylene dichloride, ethanol, isopropanol, butanol and formamide.

The top coating solutions are applied with the air suspension coating machines, such as illustrated by Wurster in the J. A. Ph.A., Scientific Edition, August 1959, at page 451. By use of the air-suspension machine, tablets or other solid substances (e.g., small particles and granules) are suspended and tumbled in a current of air with the coating composition being blown into the system. The compositions used in the top layer have a particular advantage for use in this system in that the rotating substances do not stick together during the coating process.

The following examples illustrates the best mode contemplated by the inventor for carrying out the invention but are not to be constructed as limiting the scope thereof.

Example 1

Coating compositions for the first (inner) coat of the present invention are prepared from the following types and amounts of ingredients:—

	A	
Sucrose	190	kg.
Gelatin	10.2	kg.
Sodium benzoate	638	gm.
Distilled water	95	kg.

	B	
Sucrose	1.5	kg.
Distilled water	1	kg.

	C	
Sucrose	2	kg.
Distilled water	1	kg.

D

Sucrose	2.5	kg.
Distilled water	1	kg.

E

Sucrose	200	kg.
Sodium carboxymethylcellulose, medium viscosity	3	kg.
Distilled water	100	kg.

F

Sucrose	200	kg.
Sodium carboxymethylcellulose low viscosity	7	kg.
Distilled water	100	kg.

G

Sucrose	200	kg.
Hydroxyethylcellulose medium viscosity	3	kg.
Distilled water	100	kg.

The foregoing compositions A through G, inclusive, are prepared by dissolving the various ingredients in the aqueous solvent.

The compositions are applied to the tablets to form the first (inner) coating by rotating the tablets in a coating pan.

Example 2

Coating compositions for the topcoating of the present invention are prepared from the following types and amounts of ingredients:—

A

Methylcellulose USP 10 cps.	88	gm.
Polyethylene glycol 1000 ...	22	gm.
F. D. and C. Yellow No. 5 ...	0.5	gm.
F. D. and C. Yellow No. 6 ...	0.5	gm.
Methanol	845	gm.
Chloroform	1267	gm.

B

Methylcellulose USP 10 cps.	88	gm.
Polyethylene glycol 400 ...	11	gm.
Polyethylene glycol 4000 ...	11	gm.
Methanol	845	gm.
Chloroform	1267	gm.

C

Methanol USP 01 cps. ...	88	gm.
Polyethylene glycol 1500 ...	22	gm.
Methanol	845	gm.
Chloroform	1267	gm.

D

Methylcellulose (28—30% methoxy- and 7—12% hydroxypropoxyl)	80	gm.
Anhydrous ethanol	500	cc.
Polyethylene glycol 400 ...	50	gm.
Imitation custard flavour ...	0.5	gm.
F. D. and C. Yellow No. 5 ...	0.5	gm.
F. D. and C. Yellow No. 6 ...	0.5	gm.
Chloroform q.s.	2900	cc.

E

Methylcellulose USP 10 cps.	54	gm.
Methylcellulose (28—30% methoxy- and 7—12% hydroxypropoxyl)	54	gm.
Polyethylene glycol 400 ...	8	gm.
Sodium saccharin	0.9	gm.
Indian Red Oxide	5.4	gm.
Anhydrous ethanol	540	gm.
Chloroform	2925	gm.

F

Methylcellulose USP 10 cps.	54	gm.
Polyethylene glycol 400 ...	6.25	gm.
Polyethylene glycol 4000 ...	6.25	gm.
Polyethylene glycol 6000 ...	37.5	gm.
Chloroform	1100	gm.
Methanol	700	gm.
Water	200	gm.

G

Methylcellulose USP 10 cps.	4	gm.
Polyethylene glycol 400 ...	0.5	gm.
Polyethylene glycol 4000 ...	0.5	gm.
Chloroform	55	gm.
Water	10	gm.
Methanol	35	gm.

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Methylcellulose 25 cps	40	gm.
Polyethylene glycol 400 ...	5	gm.
Polyethylene glycol 4000 ...	5	gm.
Chloroform	550	gm.
Methanol	350	gm.
Water	100	gm.

I

Methylcellulose, 10 cps. USP	5	gm.
Polyethylene glycol 4000 ...	0.625	gm.
Methanol	400	gm.
Chloroform	600	gm.

J

Methylcellulose 1500 cps. ...	5	gm.
Polyethylene glycol 200 ...	5	gm.
Chloroform	600	gm.
Methanol	400	gm.

K

Methylcellulose, 10 cps USP	9.5	gm.
Polyethylene glycol 1500 ...	0.5	gm.
Chloroform	650	gm.
Ethanol	350	gm.

L

Methylcellulose 25 cps. ...	40	gm.
Polypropylene glycol 400 ...	10	gm.
Chloroform	550	gm.
Methanol	350	gm.
Water	100	gm.

M

Methylcellulose 50 cps. ...	15	gm.
Polyethylene glycol 1500 ...	1.5	gm.
Methanol	375.5	gm.

M—*contd.*

Chloroform	600	gm.
Water	10	gm.

The foregoing compositions A through M, inclusive, are prepared by dissolving the various ingredients in the solvent of the composition.

The compositions are applied to the sugar coated tablets to form the outer film coating by means of an air suspension machine.

Example 3.

On hundred thousand 3/8" tablets weighing about 638 grams/thousand are coated in the following manner:—

First Coat (Sugar)

One hundred thousand uncoated tablets are placed in a coating pan and allowed to rotate. Ten applications of coating syrup of Example IA are made, each application being about 500 grams of syrup. Between each application of syrup about 500 grams of calcium carbonate are dusted on the tablets. Following the ten applications of syrup followed by dusting an additional ten applications (500 grams/application) of syrup are made without dusting. The tablets are then removed from the coating pan and dried. The tablets now weigh about 900 grams/thousand.

Alternatively, the tablets can be coated substituting an equivalent amount of the syrups of Example IB through G, inclusive, for the syrup of Example 1A.

Second Coat (Film)

Ten thousand sugar coated tablets are placed in an air suspension machine and about 9 kg. of the coating composition of Example 2A is blown onto the tablets. Following the application of the coating composition the tablets are suspended in warm dry air to dry the tablets. The coating of the tablets is completed and they are removed from the machine.

Alternatively, the tablets can be coated substituting an equivalent amount of each of the coating compositions of Example 2B through M, inclusive, for the composition of Example 2A.

The tablets thus prepared are pharmaceutically elegant in appearance and taste and do not exhibit loss of active ingredient during the coating process.

WHAT WE CLAIM IS:—

1. A tablet coated with an inner layer consisting essentially of a sugar and an outer layer consisting essentially of methylcellulose as herein defined and a polyalkylene glycol.

2. A tablet protected by a coating comprising an inner coating consisting essentially of sucrose and an outer layer consisting essentially of from about 50% to about 95% w/w of methylcelluiose as hereindefined and from about 5% to about 50% w/w of a polyethylene glycol having an average molecular weight of from 200 to 9000.

3. A tablet protected by a coating as claimed in claim 1 or 2 substantially as herein described with reference to the Examples.

4. A process for the preparation of a coated tablet as claimed in claim substantially as herein described with reference to the Examples.

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